REMARKS

Claims 1-16 are pending in the instant application. Claims 1-10 have been rejected. Claims 11-16 have been canceled. Claims 1 and 10 have been amended. No new matter has been added. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Elections/Restrictions

The Examiner has made final the restriction of the claims in this application. Therefore claims 1-10 are being considered on the merits in this application and claims 11-16 have been withdrawn from consideration. In light of the Examiner's decision and to facilitate prosecution, Applicants have canceled claims 11-16.

II. Rejection of Claims 1-10 Under 35 U.S.C. §112, second paragraph

The Examiner has rejected claims 1-10 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner suggests that claim 1 and its dependent claim, and claim 10 are drawn to a

pharmaceutical composition, and are rendered vague and indefinite because it is unclear if the pharmaceutical prevents infection of a patient or if the coating prevents infection. In an earnest effort to advance prosecution, Applicants have amended claims 1 and 10 to clarify that the coating prevents the release of the ammoniaphilic urea degrading microorganism into the patient as supported in the specification at page 16, lines 10-13.

The Examiner has also rejected the phrase "the sorbents" in claim 1, line 8 as lacking antecedent basis. Applicants have amended claims 1 and 10 to remove the term sorbent, and clarify the invention as not allowing the binding of digestive materials to the composition prior to reaching the target region, as supported throughout the specification and especially at page 16. Reconsideration and withdrawal of these rejections is hereby requested.

III. Rejection of Claims 1-3 and 6-9 Under 35 U.S.C. §103

The Examiner has rejected claim 1-3 and 6-9 under 35 U.S.C. §103(a) as unpatentable over Paul (US 6,180,099) in view of Ford (US 5,733,564).

The Examiner suggests that Ford specifically teaches that oral pharmaceutical compositions containing bacteria have a great

advantage in therapeutic utility when they are microencapsulated. It is suggested that at the time of the claimed invention one of skill would have been motivated by Ford to microencapsulate the composition of Paul for the disclosed "great advantages" in that therapeutic utility is increased.

As acknowledged by the Examiner, Paul does not teach encapsulated or enteric coatings. The Examiner suggests that Ford teaches that micro-encapsulating *Lactobacilli* to protect them from gastric juices. The Examiner suggests that it would have been obvious to encapsulate the composition of Paul, as it was common to do so, as demonstrated by Ford. Applicants respectfully disagree.

At the onset it is respectfully pointed out that claim 1 has been amended to clarify that the composition comprises a composition of a probiotic, a prebiotic, and an ammoniaphilic urea degrading microorganism with high alkaline pH stability and high urease activity, said composition being microencapsulated or enteric coated with a material designed to deliver the probiotic, a prebiotic, and ammoniaphilic urea degrading microorganism to their site of action in relatively native form without binding of digestive materials to the composition prior to reaching the target region, wherein said prebiotic ensures the viability of the probiotic, and wherein said microencapsulated or enteric coating

prevents the release of the ammoniaphilic urea degrading microorganism into the patient. Supported for this amendment is found throughout the specification and especially at pages 15-16.

To establish a *prima facie* case of obviousness under 35 U.S.C. 103(a) three basic criteria must be met. MPEP § 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all of the claim limitations.

Paul teaches a composition for promoting gastrointestinal health which may include *Lactobacillus* and *Bifidobacterium*, comprising 40-60% by weight of an immunoglobulin composition and 40-60% by weight of soluble dietary fiber. Paul teaches that the microorganisms are *intended* to bind to and inactivate foreign antigens, pathogenic bacteria, viruses, fungi, and protozoa in the gastrointestinal tract. See column 1, lines 19-35. As admitted by the Examiner, Paul does not teach any microencapsulated or enteric coating at all, and in view of the intent of the microorganisms to bind to other matter, a coating would not be suitable.

Ford teaches a coated composition particularly useful for releasing *Lactobacilli* into the body of a patient. The microencapsulated coating of the *Lactobacilli* is taught to increase their shelf life and further to release the bacteria into the intestine as the microencapsulation material is taught to lose its structural integrity.

The recited art fails to teach all of the limitations of claim 1. Neither Paul nor Ford teach composition with a microencapsulated or enteric coating which coating prevents the release of an ammoniaphilic urea degrading microorganism into the patient. Accordingly, the references fail to establish a *prima facie* case of obviousness against the pending claims.

Reconsideration and withdrawal of this rejection is respectfully requested.

IV. Rejection of Claims 1-10 Under 35 U.S.C. §103

The Examiner has further rejected claims 1-10 under 35 U.S.C. §103(a) as unpatentable over Paul (US 5,531,988), Niisato, Hider, Yatsidis and Giovannetti (Nephron 1995) in view of Chang et al.

The Examiner suggests that the cited art discloses a pharmaceutical composition comprising a probiotic, prebiotic and an

ammonia-philic urea-degrading microorganism with high alkaline stability and urease activity that is microencapsulated or enteric coated.

The Examiner suggests that Paul teaches a composition for promoting gastrointestinal health comprising an effective amount of *Lactobacillus* and *Bifidobacterium*. The Examiner further suggests that Paul teaches *Lactobacillus* and *Bifidobacteria* inhibit toxic activities of bacteria in patients with chronic kidney failure, inhibit overgrowth of gastrointestinal pathogens and reduce pathogenic microorganism titers in the gastro-intestinal tract.

The Examiner also suggests that Niisato teaches a composition containing fructooligosaccharides for preventing uremia and renal insufficiency. Yatzidis is suggested to teach locust bean gum is an efficient sorbent upon uremic substances to include urea, chloride, uric acid, creatine, ammonia, phosphorous and sodium.

Hider is suggested to teach that patients with kidney disorders who suffer from elevated phosphate levels are treated with magnesium hydroxide, aluminum hydroxide, calcium hydroxide or mixtures thereof.

Giovannetti is suggested to teach oral administration of activated charcoal for uremia treatment.

The Examiner suggests that it would have been obvious to one of ordinary skill in the art to have combined the ingredients for their known benefit. And further, that at the time of the claimed invention one of ordinary skill in the art would have been motivated by the above references to combine the instant ingredients together with a reasonable expectation of success to treat kidney diseases or uremia. The Examiner acknowledges that the references do not teach micro-encapsulated or enteric coated compositions. The Examiner suggests that Chang teaches oral pharmaceutical compositions for treating kidney failure wherein microorganisms are microencapsulated to prevent infection of a patient. The Examiner suggests that at the time of the present invention one of ordinary skill in the art would have been motivated by Chang to microencapsulate the composition obtained by the combined teachings above with a reasonable expectation of preventing patient infection and effectively treating kidney failure, diseases and uremia.

Applicants respectfully disagree and traverse this rejection.

It is respectfully pointed out that claims 1 and 10 have been amended to clarify that the probiotic is present in the composition with the prebiotic so that the prebiotic ensures the viability of the probiotic. Support for this amendment is found throughout the

specification and in particular at pages 10, lines 16-20. Claims 1 and 10 have been further amended to clarify that the microencapsulated or enteric coating prevents the release of the ammoniaphilic urea degrading microorganism into the patient, as supported in the specification at page 16, lines 10-13.

The Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966), stated that under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. The Supreme Court reaffirmed and relied upon the *Graham* three pronged test in its consideration and determination of obviousness in the fact situations presented in *Sakraida v. Ag Pro, Inc.*, 425 U.S. 273, 189 USPQ 449, *reh'g denied*, 426 U.S. 955 (1976) and *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 163 USPQ 673 (1969). In each case, the Court discussed whether the claimed combinations produced a "new or different function" and a "synergistic result".

As acknowledged by the Examiner, none of the prior art recited teaches a composition of a probiotic, a prebiotic, and an

ammoniaphilic urea degrading microorganism being microencapsulated or enteric coated with a material designed to deliver the probiotic, the prebiotic, and ammoniaphilic urea degrading microorganism to their site of action in relatively native form without binding of digestive materials to the composition prior to reaching the target region. Further, none of the prior art teaches that the composition is coated to comprise both the prebiotic and the probiotic so that the prebiotic ensures the viability of the probiotic, and wherein said microencapsulated or enteric coating further prevents the release of the ammoniaphilic urea degrading microorganism into the patient.

Both the scope and content of the present invention is different than the prior art recited alone, or in combination. The probiotic and prebiotic of the present invention are both included in the composition of the present invention for their unique synergistic interplay. As recited on page 10, starting at line 11, the probiotic restores normal balance between beneficial bacteria and detrimental bacteria, removes excess urea-waste product of normal protein metabolism thereby reducing the burden on ailing kidneys and removes ammonia to avert mental retardation and related conditions. The prebiotic stimulates beneficial bacterial populations. The prebiotic also ensures the viability of the

probiotic so that nitrogen sources such as urea and ammonia are effectively utilized. There is no teaching or suggestion in any of the recited prior art which would motivate one of skill to combine the probiotic with the prebiotic in a coated composition for their synergism.

As set forth in MPEP 2141, when applying 35 U.S.C. 103, the following tenets of patent law must be adhered to: (a) the claimed invention must be considered as a whole; (b) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination; (c) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and (d) reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed Cir 1990).

The Examiner has suggested that Paul teaches a composition for promoting gastrointestinal health comprising *Lacotobacillus* and

Bifidobacterium. At column 14, the composition of Paul is taught as useful for treating diarrhea, constipation and other types of gastrointestinal distress. One of skill in the art would not expect that the composition of Paul would be successful for treating uremia and kidney diseases based on this teaching.

Niisato et al. are suggested to teach a composition containing fructooligosaccharides for preventing uremia and renal insufficiency. The Examiner infers that the composition acts as a prebiotic. However, the abstract by Niisato et al. teaches only one specific fructooligosaccharide composed of 1-kestose, nystose and 1F fructofuranosyl nystose which functions as a diuretic useful to ameliorate edema. There is no suggestion that the composition functions as a prebiotic, nor is there any teaching that it would exhibit a synergistic effect with any probiotic to treat uremia. Thus, considered as a whole it does not suggest the desirability and thus the obviousness of a combination with a probiotic. Further, there is no suggestion that a coating would be at all useful in this composition.

None of the recited prior art teaches the synergistic result of a coated composition comprising a probiotic with a prebiotic for treating uremia wherein the prebiotic is useful to ensure the viability and the probiotic.

The Examiner suggests that Chang provides the necessary motivation or teaching to microencapsulate or enteric coat a composition such as the present invention. Applicants disagree. First, the microencapsulation of Chang as taught on page 1, lines 22-25 does not ensure that the patient will not be infected with the microorganism. Second, there is no motivation to combine the teachings with other prior art references. Chang teaches a microencapsulated genetically engineered bacteria for removal of urea and ammonia (see page 1, lines 28-32) which is intended to be used in lieu of traditional approaches to urea and ammonia removal. At page 2, lines 12-15, Chang states that oxystarch and urease zirconium phosphate treatment to remove unwanted metabolites were unsuccessful as the amounts were too large for the use in routine treatment of patients. There is no motivation or teaching to combine the coating of Chang with the other cited prior art. Even assuming arguendo that such a combination were proper, it does not remedy the lack of teaching to combine a prebiotic and probiotic in a coated composition so that they reach their site of action in relatively native form without binding of digestive materials to the composition prior to reaching the target region.

Thus, even if all of the recited references were combined, they would not teach or suggest all of the limitations of the

claimed invention. Namely, there is no teaching of a coated composition comprising a probiotic and a prebiotic as recited in claims 1 and 10. As claims 1 and 10 are non obvious under 103 any claims depending therefrom must also be deemed non-obvious.

Additionally, the remaining individual references which were recited by the Examiner as pertinent art to the dependent claims, actually teach away from their combination or use in a composition for treating uremia patients.

While Yatzidis et al. do teach that locust bean gum is a sorbent upon uremic substances including urea, they also teach that ingestion of locust bean gum is impracticable because it swells in the mouth and the esophagus (see page 105). Thus one of skill in the art would not be motivated to use locust bean gum for a pharmaceutical composition due to this stated impracticality.

Further, contrary to the Examiner's suggestion that Hider et al. teach that patients with kidney disorders are treated with phosphate adsorbents magnesium hydroxide, aluminum hydroxide, calcium hydroxide or mixtures thereof, they actually teach that the use of magnesium or calcium hydroxide can lead to acute side effects (see column 1, lines 17-19). Furtner, treatment with aluminum hydroxide or related preparations is taught to lead to gradual accumulation of aluminum in body tissues which must be

removed by administration of desferrioxamine. Constant use of desferrioxamine to reduce aluminum levels is taught to lead to undesirable side effects (see column 1, lines 25-34). The object of Hider et al is to refrain from using magnesium hydroxide, aluminum hydroxide, and calcium hydroxide. Thus, one of skill would not be motivated to utilize magnesium hydroxide, aluminum hydroxide, or calcium hydroxide as sorbents in a pharmaceutical composition for urease reduction.

Giovanneti is merely an abstract suggested to teach oral administration of activated charcoal for treating uremia. There is no motivation or suggestion to combine the teaching with any of the other references.

MPEP § 2143 and the Courts are quite clear; both the teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). The cited combination of prior art fails to provide this reasonable expectation of success. It is only with the instant specification in hand, which demonstrates the efficacy of Applicants' invention that one of skill could even suggest a reasonable expectation of success.

Therefore, withdrawal of this rejection is respectfully requested.

V. CONCLUSION

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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